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ART UNIT	PAPER NUMBER
1642	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/653,961	Applicant(s) WU, GUANG-JER	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5 and 7-20* is/are pending in the application.

4a) Of the above claim(s) *13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5,7-12 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *2-5 and 7-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed on September 10, 2001 is acknowledged and has been entered. Claims 1 and 6 have been canceled. Claims 3-5 and 7-10 have been amended. Claim 20 has been added.

2. Claims 2-5 and 7-20 are pending in the application. Claims 13-19 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

3. Claims 2-5, 7-12, and 20 are currently under prosecution.

Claim Rejections Maintained and Response to Applicants' Remarks

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2-5 and 7-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying the metastatic potential of a prostate cancer cell line that expresses the gene encoding MUC18 (SEQ ID NO: 2), does not reasonably provide enablement for a method of identifying the metastatic potential of *any* prostate cancer cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reason set forth in the previous Office Action.

Applicant's arguments filed September 10, 2001 in Paper No. 8 have been fully considered but they are not persuasive. In response to the previous Office Action, Applicants' argue that the amendment adding claim 20 obviates the grounds of the

rejection of the claims under 35 USC § 112, first paragraph. Also, Applicants' assert that the claimed method as amended is to be used to identify the metastatic potential only when a prostate cancer cell expresses a higher level of the MUC18 than normal prostate cells. This argument, however, is not persuasive since as discussed in the previous Office Action, it is evident that one skilled in the art cannot predict whether the invention can be used to determine the "metastatic potential" of every prostate cancer cell. Certainly, in the absence of working exemplification that is commensurate in scope with the claims, one skilled in the art would not accept the assertion that the claimed invention can be used with a reasonable expectation of success without having to first perform extensive and undue experimentation. As stated in the previous Office Action, the teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims, because certainly the method cannot be used to identify a prostate cancer cell with metastatic potential that does not express the gene encoding MUC18. Even so, it was also stated in the previous Office Action that there are clear indications in the art that not all metastatic cancer cells express MUC18, and if this is so, in the absence of working exemplification, it is not clear that the invention can always be used to identify the metastatic potential of all types of prostate cancer in all patients. The art suggests that, regardless of the type of cancer, there is an uncertainty that every tumor biopsy from each different patient, though diagnosed with the same type of metastatic cancer, will test positive for MUC18 expression. As a consequence, the results of an analysis according to the claimed method may be highly unreliable and without factual evidence to the contrary, the skilled artisan would have cause for a reasonable doubt as to whether the invention can be used clinically to successfully determine the metastatic potential of a prostate cancer cell isolated from a patient. Furthermore, as stated in the previous Office Action, there are obviously other factors that contribute to the development of metastatic phenotype. Certainly, in view of the biologic complexity of gene expression that leads to the development of the metastatic phenotype in cancer cells, the demonstration in the specification that a single cell line that lacks MUC18 is not metastatic is insufficient to prove that the invention is enabled.

Applicants state, "The present application does not teach that if a cancer cell does not express MUC18 it does not have the potential to metastasize, or even that it is not already metastatic. Instead, claim 20 (amended version of the as-filed claim 1) teaches that the claimed method is applicable if a prostate cancer cell expresses the gene encoding MUC18 higher level than a normal prostate cell, the prostate cell is more likely to have metastatic potential" (page 5, paragraph 4). Firstly, a claim cannot teach what the specification does not. Secondly, the claims are drawn to a method for identifying the metastatic potential of a prostate cancer cell expressing the gene encoding MUC18, not a method for determining if a prostate cancer cell is more likely to have metastatic potential than a normal prostate cell. Of course, a prostate cancer cell is more likely to have metastatic potential than a normal prostate cell regardless of whether or not the prostate cancer cell expresses a higher level of MUC18 than the normal cell because by definition, the cancer cell has metastatic potential and the normal cell does not. Even so, Applicants' statement appears to indicate that the invention cannot be used successfully in every case since Applicants' statement infers that the invention cannot always be used; yet the specification does not teach in which patients the method may be useful or how such patients can be identified. Essentially, Applicants are extending an invitation to the skilled artisan to measure the levels of expression of the gene encoding MUC18 in both normal and tumor tissue isolated from a patient and if the level of MUC18 is higher in the tumor than in the normal tissue, then, the invention can be used and presumably if the level of MUC18 in the tumor is lower or the same as in the normal tissue, then, the invention cannot be used.

On page 6, paragraph 2, Applicants appear to argue that the findings of Filshie, et al would not serve as a suggestion or motivation for one skilled in the art to make the claimed invention; however, the instant rejection is made under 35 USC § 112, first paragraph for lack of an enabling disclosure and if, in fact, the teachings of Filshie, et al would serve to dissuade the skilled artisan from the use of the invention, this is indeed pertinent to the question of whether the disclosure is enabling. As stated in the previous Office Action, the teachings of Filshie, et al provide factual evidence of the unpredictability associated with the relationship between "metastatic potential" and the

level of expression of MUC18, which Applicants also seem to recognize based upon their statements. Furthermore, the fact that "the MUC18 expression is expected to vary depending upon the cell types analyzed" (page 6, paragraph 2) supports the Examiner's position, which is that the variability in level of expression of the gene encoding MUC18 in metastatic cells precludes the use of determining the metastatic potential of cancer cells by measuring the level of expression of the gene encoding MUC 18 and comparing the level of expression in the cancer cell to the level of expression the gene in a normal cell. Contrary to Applicants' assertions, the Examiner is justified in cited the teachings of Filshie, et al and Shih, et al, because both Filshie, et al and Shih, et al teach that the level of expression of the gene encoding MUC18 does not correlate with metastatic potential, a fact which necessitates a more thorough correlative study designed to determine whether the invention can be used to assess the metastatic potential of prostate cancer cells. While clearly one skilled in the art cannot predict whether the invention can be used successfully, the teachings of Filshie, et al and Shih, et al serve to suggest that it is more likely that the invention will not be used successfully.

Applicants also argue, "The present invention provides an improved prognostic test for prostate cancer" (page 7, paragraph 1); however, the specification does not teach a correlation between the level of expression of the gene encoding MUC18 in a tumor specimen isolated from a patient and the patient's prognosis. Furthermore, it is not clear how the claimed method represents an improvement or to which prognostic test the disclosure of the invention supposedly provides such improvement. At any rate, it is apparent that the claims are not drawn to an improved method *per se*.

With regard to the apparent discrepancy in the teachings of US Patent No. 6,184,043-B1 and the specification, Applicants argue, "The most relevant data for the claimed invention are the results by the inventors" (page 7, paragraph 2). However, there is no reason to suspect that the method of US Patent No. 6,184,043-B1 is any less sensitive than either the Northern or Western analysis used by Applicants to determine the expression of MUC18 by the metastatic prostate cancer cell line DU-145. Therefore, aside from Applicants' unsubstantiated opinion, one skilled in the art would have no reason to discount the teachings of the art in favor of the teachings of the

specification and the apparent discrepancy remains. Nevertheless, it noted that the claims are drawn to a method for detection similar to the antibody-based method used by US Patent No. 6,184,043-B1; so if Applicants were suggesting that such a method for detection could not be used, such an assertion would obviously be at odds with the claims.

Perhaps the strongest reason that the specification is considered to provide insufficient guidance to use the claimed invention, however, is that the specification does not disclose the expression level index that would be essential to enable one skilled in the art to practice the invention with a reasonable expectation of success without having to perform undue experimentation. The skilled artisan cannot predict the threshold value that would serve to delineate the level of expression of the gene encoding MUC18 that is indicative of metastatic potential. Clearly in view of the teachings of Filshie, et al and Shih, et al, it is evident that one skilled in the art would have to perform undue experimentation first to determine if in fact, the level of expression of the gene encoding MUC18 correlates with the metastatic potential of a given cancer cell by performing statistical analysis of several replicated experiments using tumor specimens having variable metastatic potential, which have been derived from various patients, then to determine the value of this threshold, and finally to validate the use of the claimed method in a clinical setting.

In summary, Applicants' arguments have been fully considered but not found persuasive since based upon the teachings of the specification, one skilled in the art would be unable to practice the claimed invention with a reasonable expectation of success without having to first perform extensive and undue experimentation. Thus, the disclosure fails to meet the enablement requirement of 35 USC § 112, first paragraph.

6. Claims 2-5 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying the metastatic potential of a prostate cancer cell line that expresses the gene encoding the MUC18 polypeptide (SEQ ID NO: 2) using an antibody capable of specific binding to the middle portion of the MUC18 polypeptide (SEQ ID NO: 2), which spans amino acid residues 631 to 1128

of SEQ ID NO: 2, does not reasonably provide enablement for a method of identifying the metastatic potential of a prostate cancer cell that does not express the gene encoding MUC18 using *any* antibody made in an experimental laboratory animal in response to a MUC18 antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reason set forth in the previous Office Action.

Applicant's arguments filed September 10, 2001 in Paper No. 8 have been fully considered but they are not persuasive. The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims, because the method cannot be practiced with any antibody made in an experimental laboratory animal in response to a MUC18 antigen. Clearly, there is a high level of unpredictability in the art because noted in the previous Office Action, two independent investigators unexpectedly found that antibodies made in experimental laboratory animals in response to a MUC18 antigen were incapable of detecting malignant prostate cancer or melanoma cells. In light of the teachings of the references cited above, certainly the skilled artisan cannot predict whether an anti-MUC18 antibody can be used in the claimed method to reliably and accurately identify the metastatic potential of prostate cancer cells. Because the claims embrace an embodiment in which the invention can be used clinically, there is an obvious danger associated with using a method that is not fully reliable and accurate since clearly a misdiagnosis would cause grave consequences to the patient.

Additionally, as previously noted, claim 4 does not require that the antibody actually recognize and bind specifically to an epitope of MUC18, only that the antibody be made in response to a MUC18 antigen. If the antibody does not bind specifically to MUC18 or if it cross-reacts with other antigens, and if the cells expressing the cross-reactive antigens are normal and non-metastatic, the identification of metastatic prostate cancer cells will be obviously erroneous or unduly complicated by non-specific staining or background.

In view of the above and particularly in the absence of sufficient guidance with regard to these issues and because of a lack of exemplification that is commensurate in scope to the claims, one skilled in the art cannot practice the invention, when drawn to the full breadth of the claims, with a reasonable expectation of success without undue experimentation.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2-5, 7-12, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for a reason stated in the previous Office Action.

Specifically, claims 2-5, 7-12, and 20 are vague and indefinite because claim 20 recites the term "metastatic potential". The term renders the claim vague and indefinite because the term is not specifically defined in the specification and it cannot be ascertained what specific properties of a prostate cancer cell define the claimed potential for metastasis. It is well known in the relevant that the potential to metastasize can be defined differently. While malignant cancer cells generally have the capacity to metastasize, spreading from the site of primary disease to remote or secondary anatomical sites, there are several indices that the artisan might use to assess this capacity (i.e., potential), including, but not limited to *in vitro* assays measuring the motility of cancer cells, *in vitro* assays measuring the ability of cancer cells to invade subjacent monolayers, and *in vivo* assays in which immune-compromised mice are inoculated with tumor cells and metastases are histologically detected. Therefore, because the meaning of the term "metastatic potential" is not immediately apparent from reading the claim and because the specification does not specifically define the term, one of ordinary skill in the art is not reasonably apprised of the scope of the invention.

In response Applicants argue that the term "metastatic potential" is intended to mean what is readily understood by a person of ordinary skill in the art; however, the

term "metastatic potential" would not be understood by one of ordinary skill for the reason set forth in the paragraph above. In their remarks on page 9, Applicants provide the following definitions: " 'Metastasis' is defined as the shifting of a disease or its local manifestations, from one part of the body to another.... And the term, 'potential' is defined as capable of doing or being, although not yet doing or being, possible but not actual". According to Applicants, then, a cell having metastatic potential is defined as having the potential to metastasize but which has not metastasized. Of course, one cannot know whether a cell will actually metastasize until it has done so; thus, it would be necessary to have a more tangible definition of metastatic potential (e.g., having a relatively increased invasiveness or motility) so that one of ordinary the art would be reasonably apprised of the metes and bounds of invention. Also, it is noted that specification does not actually provide any factual evidence that would support the assertion that higher levels of expression of MUC18 correlate with increased metastasis, i.e., an increased frequency of shift in the disease from its local manifestation to another part of the body of a patient. Therefore, in view of Applicants' proffered definitions, it is difficult to appreciate that the invention is supported by a credible utility, but it fairly clear that the disclosure is not sufficiently enabling since one would not know how to use the invention because the metastatic potential of a prostate cancer cell, as defined by Applicants, is not a tangible quantity, which can be measured.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 2-5 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Rubenstein, et al (*Prostate* **14**: 383-388, 1989), as evidenced by Shih, et al (*Cancer Research* **54**: 2514-2520, 1994), Liu, et al (*Hinyokika Kiyo Acta Urologica Japonica* **39**:

439-444, 1993), and the annotation that accompanies the MUC18 amino acid sequence entry (Accession No. P43121) in the Swiss Protein Database (see result 1 of the US-09-653-961-2.rsp search report) for the reason stated in the previous Office Action.

Applicants traverse the rejection of claims 2-5 and 20 under 35 USC § 102(b) for the reason set forth in the previous Office Action. Specifically, Applicants state, "the value of Leu-7 immunoreactivity used to determine MI in the cited reference was obtained from the mononuclear cell staining rather than that of the prostatic epithelium (see page 386, third to fifth lines under the Results heading)" (page 10, paragraph 3). On the basis of this mistaken interpretation of the teachings of Rubenstein, et al, Applicants contend, "these studies do not provide any connection between the level of MUC18 expression and metastasis of prostate cancer cells" (paragraph bridging pages 10 and 11) and "[t]herefore the claimed invention is distinct from the method taught by Rubenstein et al" (page 11, paragraph 1). Nonetheless, on page 10 of the remarks, Applicants concede,

> [T]he Rubenstein reference teaches how to apply the immunohistologic staining to develop a malignant index (MI) to aid in distinguishing benign from malignant prostate tissue. The malignant index was determined based on the reactivity of several commercially available antibodies against certain antigens on a scale of 0-5 in a given tissue. One of the antibodies used was Leu-7. The Leu-7 antigen is an epitope in the MUC18 polypeptide.

Applicants have mistakenly interpreted the teachings of Rubenstein, et al and erroneously concluded that Rubenstein, et al did not teach that the malignant index is calculated after detection and enumeration of the various tumor-associated antigens, including the NK cells marker, which is otherwise known as Leu-7 (i.e., MUC-18), in prostate tissue. However, clearly the method of Rubenstein, et al requires the detection and enumeration of the Leu-7 (i.e., MUC-18) in prostate tissue; otherwise, it, of course, would not be possible to distinguish benign prostate tissue from malignant prostate tissue, as is the objective of the method. The reference explicitly states that eight BPH and 23 CAP specimens "were sectioned and stained using commercially prepared antisera against cytokeratin (Cyto P, Cyto M), epithelial membrane antigen

(EMA), NK cells (Leu-7), prostatic acid phosphatase (PAP), and prostate specific antigen (PSA)" (page 383, paragraph 2). Additionally, the reference explicitly teaches, "the Leu-7 antisera, originally developed as a marker for NK cells, has been shown to cross-react with prostatic epithelium" (page 384, paragraph 2). In Table II on page 386, the reference teaches the results of the staining, specifically disclosing the mean degree of marker reactivity for both BPH and CAP using the antibody that binds the NK cells marker, Leu-7. Apparently, Applicants had mistakenly interpreted the disclosure on page 386 to which they refer in their remarks to mean that the reactivity of the NK cells marker, Leu-7 is determined only on mononuclear cells and not on the prostatic tissue specimens. To the contrary, the reference teaches that the degree of reactivity measured on mononuclear cells (i.e., NK cells) is used to normalize the degree of reactivity measured on the prostatic tissue specimens. In the case of the other markers, Rubenstein, et al teach that the degree of reactivity of the markers on normal prostatic epithelium is used to normalize the degree of reactivity of the markers on the BPH and CAP specimens. Therefore, as Applicants have conceded, Rubenstein, et al teach a method for determining whether a prostate cancer cell has the potential to metastasize by calculating the "malignant index" of prostate specimens. Because as Applicants state, Leu-7 is an epitope of MUC-18, the method of Rubenstein, et al comprises detecting the expression of MUC18 coding sequence in the prostate cancer cell.

In summary, Applicant's arguments have been fully and carefully considered but have not been found persuasive and therefore the rejection of claims 2-5 and 20 under 35 USC § 102(b) for the reason stated in the previous Office Action is maintained.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 2-5 and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubenstein, et al (*Prostate* **14**: 383-388, 1989) in view of Liu, et al (*Hinyokika Kiyo Acta Urologica Japonica* **39**: 439-444, 1993), Shih, et al (*Cancer Research* **54**: 2514-2520, 1994), US Patent No. 5,807,978 A, and in further view of US Patent No. 6,057,105 A, and as evidenced the annotation that accompanies the MUC18 amino acid sequence entry (Accession No. P43121) in the Swiss Protein Database (see result 1 of the US-09-653-961-2.rsp search report) for the reason stated in the previous Office Action.

Applicants traverse the rejection of claims 1-12 under 35 USC § 103(a) arguing that Rubsenstein, et al "does not teach the use of anti-MUC18 antibody as taught in the present application" (page 11, paragraph 3). However, for the reason stated above, the basis of this argument is a mistaken interpretation of the teachings of Rubenstein, et al and therefore is not persuasive.

Additionally, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Finally, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be

established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, apart from the reason already of record, Rubenstein, et al teach that their findings "suggest that the MI recognizes those tissue markers that are associated with the malignant state" (paragraph bridging pages 386 and 387). Furthermore, Rubenstein, et al teach, "To test this theory, a mean MI was determined for nine patients who had a histologic diagnosis of prostatic atypical hyperplasia. The mean MI generated of 3.0 was significantly greater ($P < .01$) than that encountered in BPH (Table III)" (page387, paragraph 1). Therefore, Rubenstein, et al conclude:

> The MI demonstrates that under standardized conditions, and using multiple markers as contributory factors, the acknowledged inconsistencies encountered in evaluation of individual slides using singular antisera can be normalized. Generation of such an index, which this formula yields only minimal overlap between pathologic classifications, also allows one to focus on those markers that are most effected by the transformational event and possibly those that precede it. The MI is therefore a tool that may be used to identify those alterations in tissue organization that should be more closely investigated, such as the development of histologic prostatic atypical hyperplasia.

With regard to the teachings of Liu, et al, Applicants argue, "Liu et al. teaches the opposite of what the claimed invention teaches; longer survival time and interval free of progression were observed in prostate cancer patients showing higher HNK-1 expression (e.g., Leu-7, an epitope of MUC18)" (emphasis in the original) (paragraph bridging pages 11 and 12). In response to this assertion, first it is noted that the invention cannot teach, rather the disclosure teaches. Nevertheless, the teachings of Liu, et al are not necessarily contrary to the disclosure since Liu, et al correlated the percentage of tumors cells expressing HNK-1/Leu-7 and the patient's prognosis. Clearly, Liu, et al did not teach that a higher level of expression of HNK-1/Leu-7 correlates with decreased metastatic potential; therefore, Liu, et al did not teach the opposite of that which Applicant has disclosed in the specification. Furthermore, the results to which Applicant refers in the remarks were acquired by the analysis of tumor

specimens collected from patients with *metastatic stage D2* prostate cancer; therefore, even though Liu, et al found that longer survival times and intervals free of disease progression were observed in patients with tumors showing a higher percentage of cells staining positively for HNK-1/Leu-7, because the tumors were already metastatic, this finding certainly cannot be a reflection of metastatic potential.

In summary, Applicant's arguments have been fully and carefully considered but have not been found persuasive and therefore the rejection of claims 2-20 under 35 USC § 103 for the reason stated in the previous Office Action is maintained.

New Claim Objections

13. Claim 2 is objected to because the claim depends from canceled claim 1. Appropriate action is required.

New Claims Rejections

Claim Rejections - 35 USC § 112

14. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite because the claim recites the limitation "wherein the MUC18 antigen is a middle portion of the MUC18 coding sequence consisting of the amino acid sequence as set forth amino acid residues 211-376 of SEQ ID NO:2". Recitation of the limitation renders the claim indefinite because the middle portion of the MUC18 coding sequence would not consist of an amino acid sequence; rather the coding sequence would consist of a polynucleotide sequence that encodes an amino acid sequence. Additionally, the MUC18 antigen according to claim 5, which is a coding sequence (i.e., nucleic acid), would not be expected to elicit the production of an antibody that could be used in the method of claim 3. Finally, it is unclear what is meant by the phrase "the amino acid sequence as set forth amino acid residues 211-376 of SEQ ID NO:2".

Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Conclusion

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. This application contains claims 13-19 drawn to an invention non-elected with traverse in Paper No. 5. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 3, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600